

## Review

# Emerging roles of lncRNA in Nasopharyngeal Carcinoma and therapeutic opportunities

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## Abstract

Nasopharyngeal carcinoma (NPC) is a kind of malignant tumor with ethnic and geographical distribution characteristics. However, the molecular mechanisms of NPC are still unclear. Long non encoding RNAs (lncRNAs) are becoming important regulators in gene expression networks, including post transcriptional and post translational regulation of protein, protein complex organization, signal transduction and recombination among cells, which are involved in cancer recognition. Recent evidence shows that lncRNAs play important roles in the occurrence and development of NPC. Therefore, in-depth understanding of abnormal lncRNAs will provide new understanding of the pathogenesis in NPC, and provide new tools for the early diagnosis and treatment of NPC. This article reviews the abnormal lncRNAs in NPC cells and the roles of lncRNAs in the tumorigenesis of NPC. In addition, we also discuss the diagnostic and therapeutic potential of lncRNAs in NPC.

Key words: Long-non-coding RNAs; Nasopharyngeal Carcinoma; emerging roles; therapeutic opportunities

## Introduction

Nasopharyngeal carcinoma (NPC) is a unique malignant tumor of the head and neck, which originates from the epithelial of the nasopharyngeal mucosa. Nevertheless, the global incidence rate is uneven. Over 70% of new cases occur in East Asia and Southeast Asia[1]. The exact etiology of NPC remains unclear, but risky factors recognized include Epstein Barr Virus (EBV) infection, genetic predispositions, dietary habits and environmental factors[2]. Most of them have stepped into advanced stage when they are diagnosed for the first time. So far, the intensity modulated radiotherapy (IMRT) remains the main treatment for non-metastatic nasopharyngeal carcinoma[3, 4]. The NCCN guidelines recommend concurrent chemoradiotherapy combined with adjuvant chemotherapy, or induction chemotherapy combined with radiotherapy / chemoradiotherapy for locoregionally advanced NPC (T1, N1-3; T2-T4, any N)[5]. Although the survival rate of early NPC after radiotherapy and chemotherapy is high, the

survival rate of patients with metastatic or recurrent NPC (IVB stage) is still low. Besides, radiotherapy or Chemoradiotherapy will cause acute and residual toxicity inevitably, such as dry mouth, sensorineural hearing loss, radiation osteonecrosis and a series of complications, leading to the decline of the life quality of patients[1]. In recent years, immune checkpoint therapy has made great progress, which is a promising method to improve clinical outcomes. Studies have shown that these patients benefit from a heterogeneous population. Thus, looking for more targeted and individual differences in treatment still has important clinical application prospects.

As we all know, RNA plays a vital role in the organization and regulation of genome through the activity of a large number of protein-coding or non-protein coding RNAs (ncRNAs). On the basis of the Encyclopedia of DNA Elements (ENCODE) project, the transcripts cover 62-75% of our genome, most of which are non-coding RNA[6]. Long

non-coding RNA (lncRNA) usually defined as non-protein coding RNA molecules longer than 200 nucleotides, is once considered as transcription "noise". However, more and more studies have shown that lncRNAs play different roles in regulating gene transcription, post transcription, post translation and epigenetic modification by interacting with DNA, RNA, protein molecules and / or their combinations during gene expression, and the abnormal expression or deficiency of them closely related to tumor occurrence and development[7-10]. In addition, evidence shows that lncRNAs can act as either tumor suppressor genes or oncogenes in tumor progression by regulating tumor suppressor or oncogenic mRNAs respectively through numerous mechanisms, including the epigenetic, transcriptional, post transcriptional regulation of relative genes, cell cycle distribution, cell differentiation, epigenetic modification control and so on[11-14]. The RNA-based therapeutics are also gradually playing roles in a variety of cancers[15]. In recent years, the occurrence and mechanism of lncRNAs in NPC have

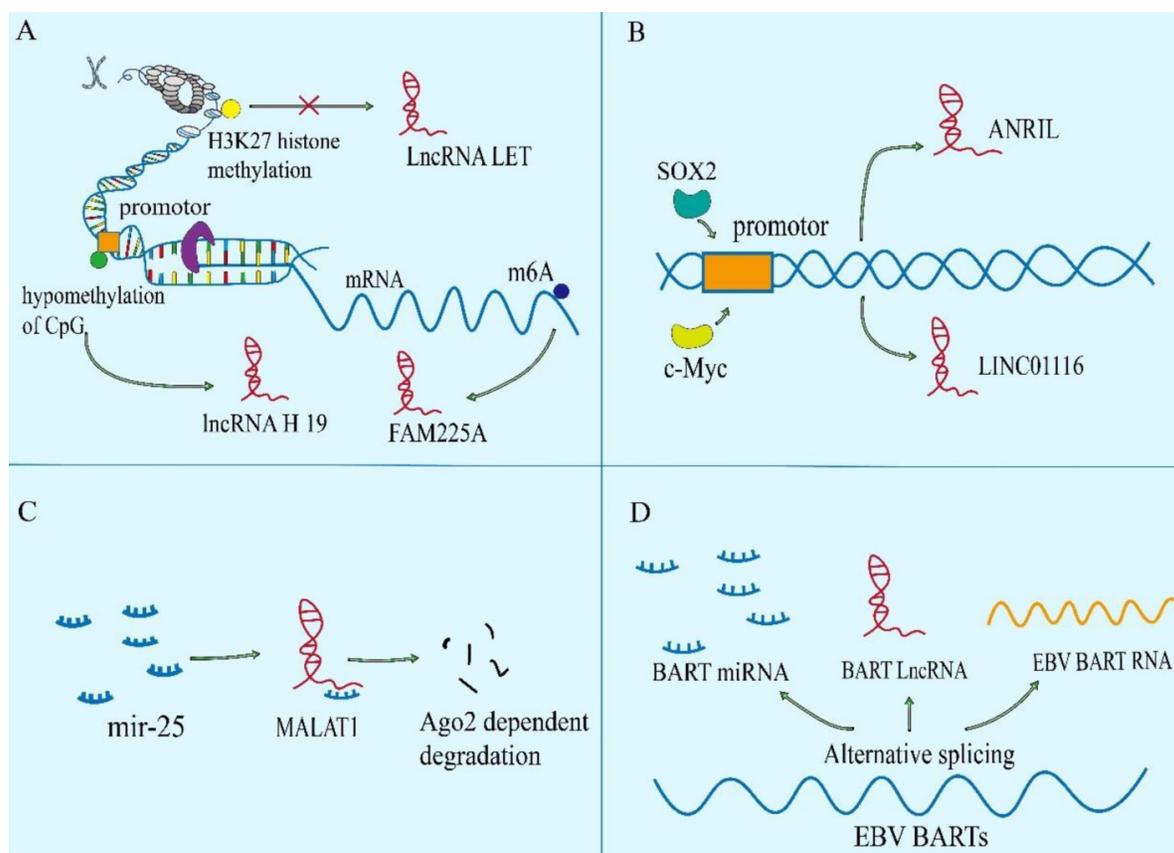
been widely studied. Many lncRNAs are maladjusted in NPC, and play important roles in the occurrence, development and even treatments of NPC. In this review, we will describe the biological role and mechanism of lncRNAs in NPC, aiming to clarify the latest research on the potential use of lncRNAs to be diagnostic / prognostic markers and therapeutic targets.

### Aberrant levels of lncRNAs in NPC

A number of genome sequencing show that some lncRNAs are dysregulated during the development of NPC. Abnormal lncRNAs biogenesis is related to the pathogenesis of NPC. The different lncRNA profiles of NPC are shown in Table 1. The imbalance of lncRNAs in the occurrence and development of NPC mainly include the epigenetic regulation, the transcriptional activation by some oncogenic transcription factors, the binding of microRNAs to lncRNAs, and the special processing methods that endow lncRNAs with carcinogenic function (Figure 1).

**Table 1.** Some dysregulated lncRNAs and their roles in the progression of NPC

lncRNAs	Roles in NPC	Biding partners	Action modes	Outcomes	Refs
HOXA-AS2	Oncogene	miR-519	miRNA sponge	↑ proliferation ↑ metastasis	[134]
AFAP1-AS1	Oncogene	KAT2B protein	Histone modification	↑ proliferation	[37]
PVT1	Oncogene	KAT2A protein	Cytoskeleton reorganization	↑ proliferation	[39]
ANCR	Oncogene	EZH2 protein	Cytoskeleton reorganization	↑ proliferation	[38]
CASC15	Oncogene	miR-101-3p	miRNA sponge	↑ proliferation ↑ metastasis	[156]
ANRIL	Oncogene	miR-125a	miRNA sponge	↑ proliferation ↓ Apoptosis	[56]
FAM225A	Oncogene	miR-590-3p miR-1275	miRNA sponge	↑ proliferation ↑ metastasis	[21]
ZNF667-AS1	Tumor suppressor	miR-1290	miRNA sponge	↓ proliferation	[157]
MEG3	Tumor suppressor	miR-21	miRNA sponge	↓ autophagy ↓ apoptosis	[158]
LINC01116	Oncogene	MYC mRNA	protein translation	↑ proliferation ↑ metastasis	[27]
NPCCAT1	Oncogene	YY1mRNA	protein translation	↑ proliferation ↑ metastasis	[58]
THOR	Oncogene	YAP protein	protein localization	↑ stemness	[59]
AWPPH	Oncogene	IGF2BP1 protein	Protein stabilization	↑ proliferation ↓ Apoptosis	[159]
DANCR	Oncogene	RBM3 protein	Cytoskeleton reorganization	↑ proliferation	[66]
LINC01133	Oncogene	YBX1 protein	sequestration of proteins	↑ proliferation ↑ metastasis	[69]
LINC00669	Oncogene	SOCS1	sequestration of proteins	↑ proliferation ↑ metastasis	[61]
LET	Tumor suppressor	ERK1/2	Protein phosphorylation	↓ proliferation ↓ metastasis	[75]
MACC1-AS1	Oncogene	miR-145	miRNA sponge	↑ stemness	[102]
FOXD1-AS1	Oncogene	FOXD1	protein translation	↑ glycolysis	[88]
TINCR	Oncogene	ACLY	Avoid ubiquitination degradation	↑ Acetyl-Coa Metabolism	[93]
HCG18	Oncogene	miR-140	miRNA sponge	↑ proliferation ↑ metastasis	[55]
EPB41L4A-AS2	Oncogene	YBX1 protein	miRNA sponge	↑ metastasis	[68]
RP11-624L4.1	Oncogene	CDK4, CDK6, and Cyclin D1	sequestration of protein	↑ proliferation	[73]
MALAT1	Oncogene	miR-124	miRNA sponge	↑ proliferation ↑ metastasis	[45]
HOTAIR	Oncogene	VEGFA mRNA	transcription	↑ Angiogenesis	[115]



**Figure 1. The regulation of the levels of lncRNAs in NPC.** **A.** The epigenetic regulation of lncRNAs: LET can be transcriptionally repressed by H3K27 histone methylation on the LET promoter. Modification of m6A in FAM225A leads to the improvement of RNA stability of it. The CpG dinucleotides within the H19 promoter region correlates with well-differentiated NPC. **B.** The transcriptional activation of lncRNAs by some oncogenic transcription factors (e.g., c-Myc and SOX2). **C.** The binding of microRNAs to lncRNAs. **D.** The special processing methods that endow lncRNAs with carcinogenic function.

## Epigenetic modification

Epigenetic regulation is the mechanism by which gene function is selectively activated or inactivated in the cells [16, 17]. Similar to mRNAs, lncRNAs can also be controlled by epigenetic regulation [18]. In NPC, abnormal chromatin marks at lncRNA genes can be found a trace (Figure 1A). The lncRNA-LET is transcriptionally repressed by H3K27 histone methylation on the LET promoter mediated by enhancer of zeste homolog 2 (EZH2) [19]. And EBV-encoded latent membrane protein 1 (LMP1) up-regulates the expression of EZH2 [20]. In addition, m6A modification in lncRNA is extremely widespread, which has been shown to participate in the occurrence and development of various cancers. In NPC, it is also found that m6A is enriched on lncRNA-FAM225A. Modification of m6A in FAM225A leads to the improvement of RNA stability, which may partially account for upregulation of FAM225A in NPC. Mechanistically, up-regulated FAM225A functions as a competing endogenous RNA (ceRNA) for sponging miR-590-3p and miR-1275, leading to the upregulation of their target integrin subunit  $\beta$  3 (ITGB3), and the activation of

FAK/PI3K/Akt signaling to promote NPC cell proliferation and invasion [21].

## Transcriptional activation

Recently, it has been reported that many transcription factors may be involved in the regulation of transcription of lncRNAs in NPC (Figure 1B), involving to c-Myc, SOX2 and androgen receptor (AR) [22-24]. For example, increased SOX2-binding activity on the ANRIL promoter induces the transcription of ANRIL [22]. Furthermore, AR is a transcription factor that acts as a steroid hormone and has been found to mediate the increased transcription of linc01503 [23]. As well as we know, the c-Myc proto-oncogene is a significant member of the Myc/Mad/Max transcription factor network, which regulates nearly 15% of genes in the human genome [25, 26], thus participating in the various pathological of tumor. It is noteworthy that c-Myc has two binding sites in the region of lncRNA-AFAP1-AS1, which can control the promoter of lncRNA-AFAP1-AS1 [24]. MYC also serves as the transcriptional activator of LINC01116 in NPC cells [27].

**miRNA sponging**

At present, the ceRNA mechanism has been studied more, but some studies have found that miRNAs can sponge lncRNAs, thereby regulating the level of lncRNAs itself by post transcriptional regulation[28, 29]. For instance (Figure 1C), elevated miR-25 in NPC cells can bind to the metastasis associated lung adenocarcinoma transcript 1 (MALAT1) for directly silencing it in an Argonaute2 (Ago2)-dependent degradation, thereby inhibiting tumor progression[28]. However, for the present, the relationship between miRNAs and lncRNAs is mainly focused on the mechanism of ceRNA, but miRNAs are another way to decrypt lncRNAs.

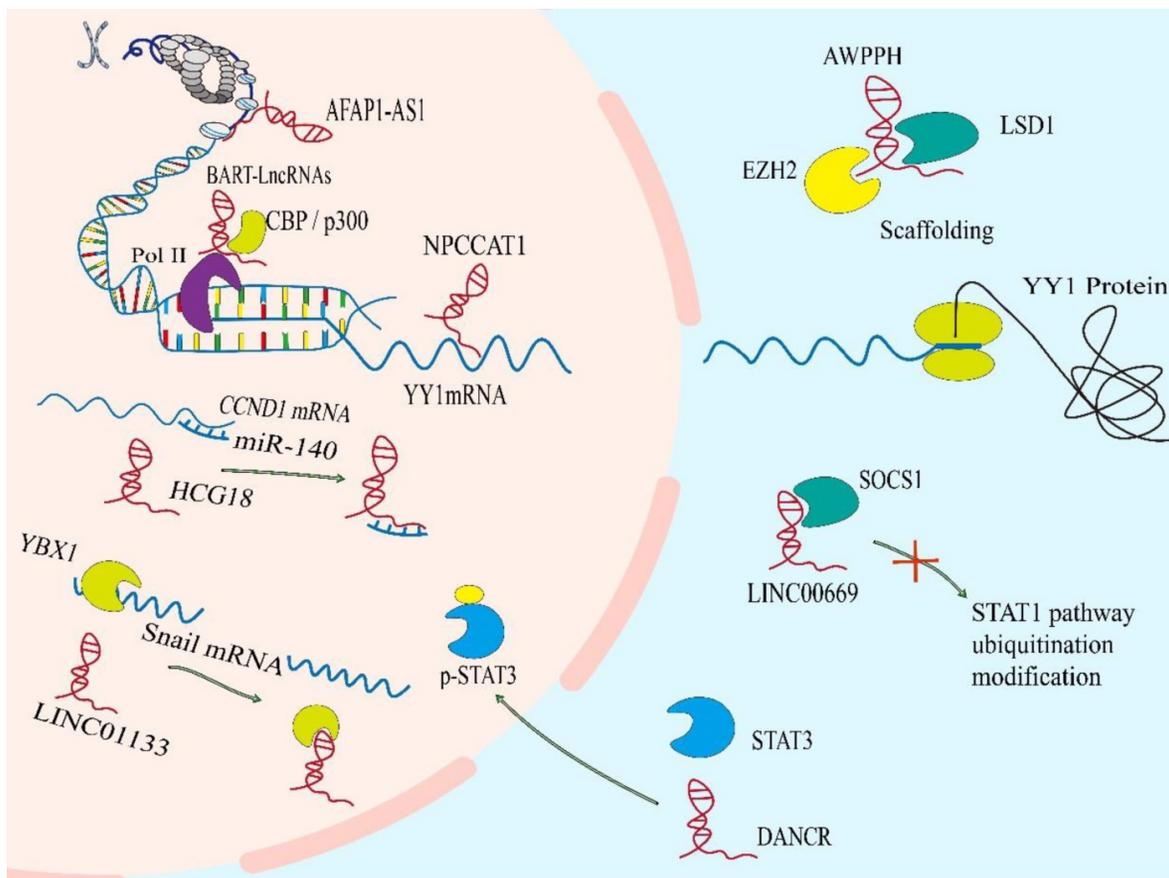
**RNA processing**

Like coding proteins, noncoding RNAs are cut and transcribed from the genome. Different splicing methods produce different functional molecules, which are partly involved in the occurrence of NPC (Figure 1D). For example, EBV BARTs comprise two groups of non-coding RNAs. One is a group of miRNAs which are produced from introns prior to splicing. And the other is a complex family of alternatively spliced polyadenylated RNAs[30].

Among the multiple splicing forms of BART RNA, lncRNA BART can regulate host gene expression, maintain EBV latency associated environment and drive carcinogenesis in NPC[31].

**Functional mechanisms of lncRNAs in NPC**

lncRNA is a class of multifunctional molecules. The versatility of lncRNA stems from several unique physical and chemical properties[32]. Firstly, and perhaps most obvious, it is the ability to pair with other nucleic acid bases. The lncRNA is particularly good at recognizing DNA and RNA targets through simple one-to-one base pairing interactions. By binding to DNA or RNA, lncRNAs can reshape chromatin structure and epigenetic modification. Furthermore, lncRNAs act as molecular sponges to interact with mRNAs or miRNAs to regulate the stability and translation of mRNAs or the binding of miRNAs to their own targets. Secondly, lncRNA molecules can be folded into three-dimensional structures of complex to provide a complex recognition surface, thus regulating the location or stability of protein via binding to it, and the formation or dissociation of protein complex, to adjust the function of it (Figure 2)[33].



**Figure 2. Functional mechanisms of lncRNAs in NPC.** The lncRNAs can reshape chromatin structure and epigenetic modification. They act as molecular sponges to interact with mRNAs or miRNAs to regulate the stability and translation of mRNAs or the binding of miRNAs to their own targets. lncRNAs can regulate the location or stability of protein via binding to it, and can also regulate the formation or dissociation of protein complex, to adjust the function of protein.

## DNA binding and chromatin remodeling

Nuclear lncRNAs have been widely observed to be associated with DNA by RNA-DNA binding. This transcriptional regulation through lncRNA-DNA interaction usually changes chromatin structure through forming RNA-DNA heterozygotes (also known as R loops)[34], which may provide signals to recruit biomolecules (for instance, epigenetic modifiers) to regulate gene expression, or to spatially aggregate promoters, enhancers or inhibitors to regulate transcriptional activity.[35, 36] The lncRNA BamHI-A rightwards transcripts (BARTs) localize within the nucleus of EBV-infected cells, and appear to stall RNA polymerase II at the promoter region of IFNB1 and CXCL to inhibit transcription. It suggests that lncRNA BART mediates epigenetic regulation of gene expression through interaction with the chromatin remodeling machinery[31]. The lncRNAs can also regulate the acetylation level of downstream gene promoters. The AFAP1-AS1 binds to KAT2B and promotes acetyltransferase activation at two residues (E570/D610). Then KAT2B further promotes H3K14 acetylation and protein binding to the bromo domain of TIF1 $\alpha$ . Consequently, TIF1 $\alpha$  acts as a nuclear transcriptional coactivator of RBM3 transcription, leading to stabilization of mRNA of YAP and enhancing NPC tumorigenicity[37]. Some lncRNAs act as cores or scaffolds. The lncRNA ANCR may act as a scaffold to stable the interaction of EZH2 and other proteins within or without PRC2 complex, which is vital in the regulation of target genes of EZH2[38]. The lncRNA PVT1 also serves as a scaffold for the chromatin modification factor KAT2A to mediate histone 3 lysine 9 acetylation (H3K9), thereby recruiting the nuclear receptor binding protein TIF1 $\beta$  to activate NF90 transcription, increasing HIF-1 $\alpha$  stability and promoting a malignant phenotype of NPC cells[39]. The hypo- and hypermethylation of CpG dinucleotides have also been demonstrated to be an important epigenetic event in the regulation of gene transcription by modifying the structure of chromatin[40]. And hypomethylation of the CpG dinucleotides within the lncRNA H19 promoter region correlates with well-differentiated NPC[41].

## Sponging mRNAs and miRNAs

It is noteworthy that specific endogenous lncRNAs containing miRNA binding sites can function as sponge for specific miRNAs and interfere with their functions, thereby regulating gene expression. Significantly, lncRNAs may interact with a tremendous amount of miRNAs and weaken their ability to bind to mRNAs[42]. Such as, SNHG1, CYTOR, MALAT1, nuclear paraspeckle assembly transcript 1(NEAT1) and so on, they all have ability to

sponge with miR-145-5p, miR-613, miR-124 or miR-204, respectively[43-46]. Mechanistically, a novel and extensive interaction network involving ceRNAs, in which lncRNAs regulate protein-coding mRNA molecules by competitively binding their target sites to miRNAs[47]. The lncRNA-miRNA axis is involved in the regulation of various cell signaling pathways, like PI3K / Akt / mTOR, Wnt /  $\beta$ -Catenin, Hedgehog, NF- $\kappa$ B, NOTCH3, Ras-MAPK, ubiquitin-specific protease 39 and so on, which are closely related to the occurrence and development of NPC[21, 48-54]. A case in point is that lncRNA HCG18 modulates Wnt/ $\beta$ -catenin and Hedgehog pathway by directly binding to miR-140 and effectively act as a ceRNA for miR-140 to increase the expression of cyclin D1, which contributes to NPC progression[55].The lncRNA ANRIL induces proliferation, inhibits apoptosis, and reduces radiosensitivity in NPC cells through sponging miR-125a[56]. In NPC, there are still many studies on ceRNA, and new lncRNAs have been reported continuously.

## Protein interaction and regulation

In addition to the regulation of gene expression events mediated by the effect of lncRNA on mRNA, the ability of lncRNAs to bind and regulate protein activity goes beyond the factors involved in transcription. These connections mainly involve in the association of lncRNAs with proteins orchestrates protein localization or stability, as well as protein complex assembly or sequestration of proteins from their own binding partners, thereby executing their biological function.

## Protein translation

Although lncRNAs do not have open reading circles for protein translation, ribosome profiling has identified ribosome-associated lncRNAs[57]. Meanwhile, many studies have showed that the distribution of lncRNAs in cytoplasm can regulate the expression of proteins via directly interacting with them[34]. The LINC01116 in the cytoplasm can enhance MYC protein translation as antisense transcripts facilitating the translation of selected mRNA in a cap-dependent manner[27]. In the same way, NPC copy number amplified transcript-1 directly binds to the 5'UTR of the mRNA of YY1, thereby inducing translation of it, which promotes NPC cell proliferation and migration[58].

## Protein localization or stability

It has been reported that the subcellular localization of many tumor-associated proteins is regulated by lncRNAs. Like the lncRNA THOR which can enhance the transcriptional activity of YAP by directly binding to YAP to inhibit translocation of it

from nucleus to cytoplasm[59]. The lncRNAs also control protein localization indirectly. The Phosphorylated STAT3 is the active form of STAT3. Overexpressed p-STAT3 is confirmed in more than 70% of NPC patients[60]. The LINC00669 can competitively bind to SOCS1, the key suppressor of JAK/STAT signaling pathway, and insulate it from imposing ubiquitination modification on the component of JAK/STAT pathway, which leads to the augment of both total and phosphorylation of STAT3, and transfers it from cytosolic into nucleus for initiating the transcription of genes concerned about proliferation and invasion in NPC[61]. Meanwhile, lncRNA DANCR seems to function as a molecular scaffold to promote STAT3 activation by facilitating JAK1 to phosphorylate STAT3 and regulate the location of p-STAT3[62].

Besides, lncRNAs mediate oncoprotein stabilization and tumor suppressor genes lead to the progression or inhibition of NPC, respectively. For instance, lncRNA AWPPH can stabilize LSD1 via interacting with a common RNA binding protein IGF2BP1, which boosts LSD1 expression in cytoplasm of NPC cells, so as to drive NPC process[63].

### Protein complex assembly

lncRNAs can also bind to proteins or protein complexes performing explicit biological functions, such as epigenetic regulation[64]. The Adenylate and uridylylate (AU)-rich elements (AREs) in the 3' regions of DANCR has strong binding ability with NF90/NF45 complex, and can interact directly with NF90/NF45 to stabilize HIF-1  $\alpha$  mRNA promoting NPC metastasis[65]. In addition, DANCR complexes with RNA binding protein 3 (RBM3) protein to stabilize SOX2 mRNA, leading to NPC cell proliferation[66]. These lncRNAs participate in the assembly of protein complex, which are more conducive to the implementation of function.

### Sequestration of proteins from their own binding partners

On the contrary, some lncRNAs act as competitive binding partners to isolate proteins from their original substrates, leading to the dissociation of protein complexes. A well-known RNA and DNA binding protein YBX1 activates *Snail* translation directly and induces epithelial-mesenchymal transition[67]. In NPC, EPB41L4A-AS2[68] and LINC01133 [69] can bind to YBX1 to sequester the mRNA of *Snail* from YBX1, thereby suppressing the expression of *Snail* and inhibiting the epithelial mesenchymal transition (EMT) process of NPC cells. And LINC00669 competitively binds to SOCS1, the key suppressor of JAK/STAT signaling pathway, to

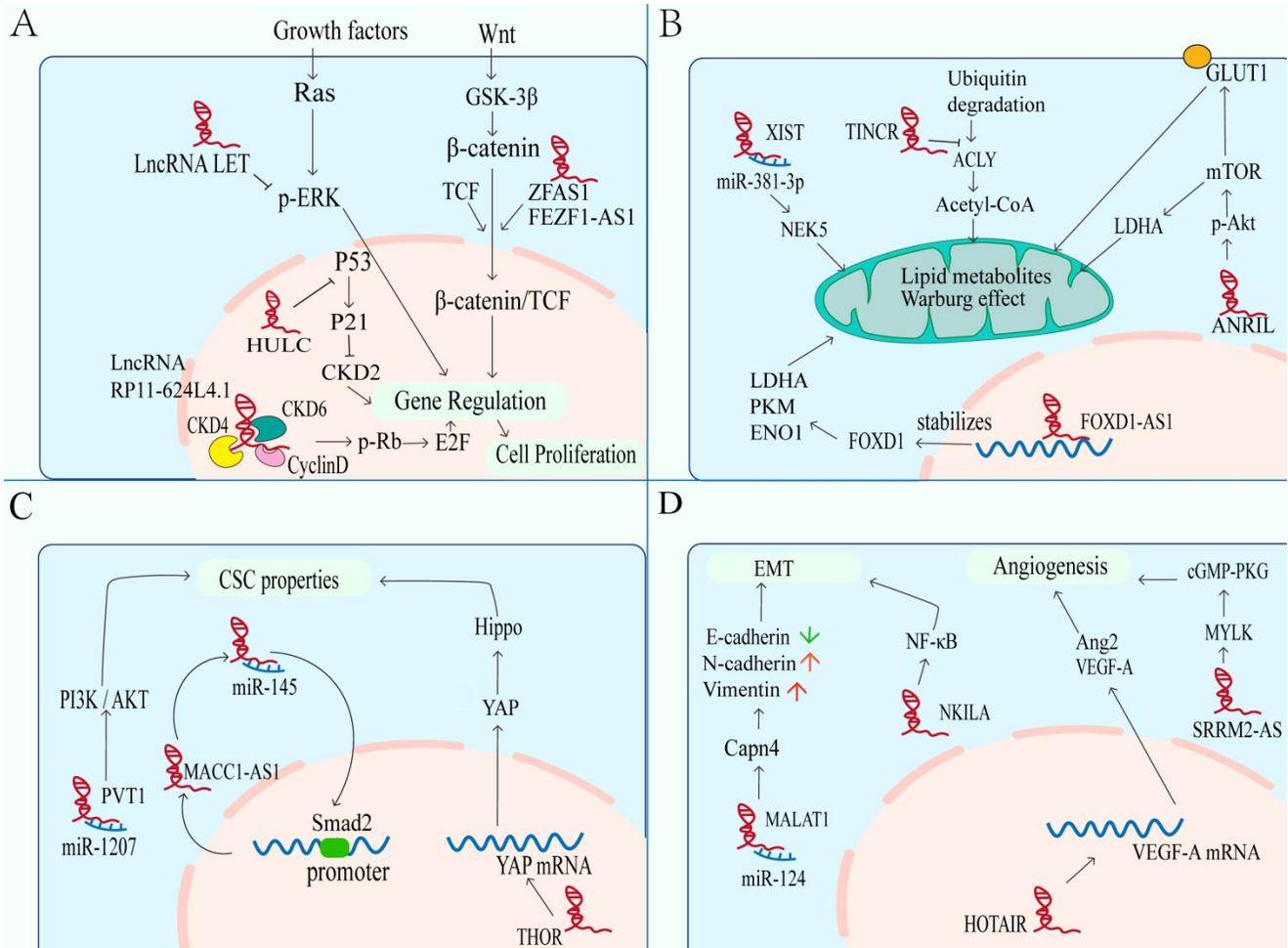
insulate it from imposing ubiquitination modification on the pathway component of STAT1, which leads to abnormal stabilization and activation of it to promote NPC cell proliferation and invasion[61].

### Significance of lncRNAs in NPC hallmarks

Different cancers have similar characteristics, such as continuous proliferation, resistance to cell death and enhancement of invasion. These characteristics are closely related to cancer behaviors[70]. NPC related lncRNAs can promote or inhibit these carcinogenic phenotypes, thus providing a reasonable treatment strategy for NPC (Figure 3).

### Sustaining proliferative signaling

One of the most remarkable characteristics of cancer cells is the growth signal of self-sufficiency, even without external stimulation. Normal cells carefully control the production of growth promoting or inhibiting factors to ensure strict control of cell number, tissue structure and function. On the contrary, tumor cells show uncontrolled growth response, which makes them more or less independent of proliferation signals, leading to unlimited expansion. In order to achieve this independence, tumor cells have the acquired ability to maintain proliferation signal transduction in a variety of ways, including the participation of lncRNAs (Figure 3A). Firstly, Cell cycle progression is essential for cell proliferation. The abnormal regulation of cyclin D1, CDK4 and CDK6 is positively correlated with the proliferation of NPC cells. The CDK4 has been identified as a major carcinogenic driver in cell cycle components, belonging to the cyclin dependent kinase family. As a G1 serine / threonine kinase, CDK4 is also an important protein for normal cell proliferation[71]. The CDK4 / cyclin D1 complex phosphorylates and inhibits the tumor suppressor protein retinoblastoma (RB), resulting in the release of E2F transcription factor, which regulates the gene expression required for S-phase entry and progression[72]. The lncRNAs can also participate in the evolution of the cell cycle regulated by CDK4/6 or Cyclin D1 in NPC. For example, lncRNA RP11-624L4.1 acting as a scaffold for CDK4, CDK6, and Cyclin D1 to form a protein complex, which promotes NPC proliferation in the CDK4/6-Cyclin D1-Rb-E2F1 pathway[73]. Secondly, the ERK1 / 2 pathway is also an important signal pathway of proliferation, which can regulate the transition of G1-to S- phase[74]. In NPC, lncRNA-LET suppresses cell growth and cell cycle by inhibiting the phosphorylation of kinase activity of ERK1/2. LET can also up-regulate cell cycle related genes, including *CDKN1A*, *CDKN1B* and *CDKN2D*, and induce cell



**Figure 3. Significance of lncRNAs in NPC hallmarks.** Nasopharyngeal carcinoma related lncRNAs can promote or inhibit carcinogenic phenotypes through distinct mechanisms. These hallmarks include: **A.** The abnormal regulation of lncRNA leads to sustaining proliferative signaling in NPC. **B.** lncRNAs are involved in dysregulated energetics caused by metabolic reprogramming. **C.** lncRNAs participate in hyperactivation of CSC-related signaling, leading to acquiring CSC properties of NPC cells. **D.** Enhanced metastasis induced by the overexpression of mesenchymal markers and the formation of additional vessels.

cycle arrest in G0 / G1 phase[75]. Thirdly, β-catenin is also a cell cycle regulator. When the Wnt signaling is abnormally activated, β-catenin protein cannot be degraded by GSK-3β, resulting in the accumulation of β-catenin in the cytoplasm or the translocation of it into the nucleus, and initiating the transcriptional regulation of downstream target genes[76]. LncRNA ZFAS1 is overexpressed in NPC to promote the occurrence of NPC by activating the Wnt/β-catenin pathway[77]. Besides, lncRNA FEZF1-AS1 also can enhance β-catenin entry of nucleus and result in a series of checkpoint proteins expressing (including CDK4 / 6, c-MYC and CyclinD1) and G1 / S phase transiting and cell growing[78]. Lastly, as well as tumor suppressor protein p53, which is a key protein in cell cycle checkpoint DNA damage detection (by inducing p21 transcription to stop cell cycle in G1 phase). The upregulated lncRNA highly upregulated in liver cancer (HULC) in NPC can inhibit the activation of p53 and down regulate the level of p21 gene, result in unlimited proliferation of tumor cells

and tumor progression[79].

**Dysregulating cellular energetics**

Metabolic reprogramming is a sign of cancers. The most obvious is that glycolysis is the main way of energy supply. Although oxidative phosphorylation can produce more ATP, cancer cells still tend to generate energy from glycolysis, which is due to proliferating cells need not only ATP, but also nucleic acids, fatty acids, proteins and membrane phospholipids. Glycolysis can provide the substrates and intermediates needed for the synthesis of these biomacromolecules to meet the needs of rapid DNA replication of tumors. This phenomenon is known as "Aerobic glycolysis "or " Warburg effect"[80-83]. An increasing evidence indicates that lncRNAs can regulate glucose metabolism in cancer cells in different ways (Figure 3B), such as directly regulating glycolytic enzymes (e.g., pyruvate carboxylase, fructose-2, 6-bisphosphatase, 6-phosphogluconate, phosphoenolpyruvate carboxy kinase and glucose

transporter GLUT), or through indirect regulation of signal transduction pathways (e.g., Wnt/Snail, JAK/STAT, p53 pathways, HIF-1 $\alpha$ , PI3K/Akt/mTOR and Ikb1-ampk pathways)[83, 84]. Glucose transporter is composed of two membrane related carrier proteins, Na + SGLTs and GLUTs[85]. Some lncRNAs regulate the glycolysis process by combining with GLUT. One example is lncRNA ANRIL promotes Akt phosphorylation and activates mTOR signaling pathway, thereby elevating the expression of GLUT1 and LDHA (key enzyme to catalyze the conversion of pyruvate to lactate in the last step of aerobic glycolysis)[86], so as to increase glucose uptake, and rapidly generate ATP for proliferation of NPC cells ultimately[87]. Another example is lncRNA FOXD1-AS1, which promotes glycolysis by maintaining the expression of FoxD1, which is related to lactate dehydrogenase A (LDHA), pyruvate kinase M2 (PKM) and enolase 1 (ENO1) genes[88].

Compared with nonmalignant cells, cancer cells not only show dysregulation of carbohydrates, but also have alterations related to lipid metabolism[89]. In fact, increased lipogenesis is considered to be a marker of many invasive cancers[90], with de novo fatty acid (FA) synthesis, for supporting membrane body biosynthesis and the energy requirement of proliferation, and for helping synthesize macromolecules in membranes and deliver lipid signals to fight pressure[90, 91]. Acetyl CoA synthesis of lipids is the most common mechanism of lipid supply in tumor cells[92]. In NPC, lncRNA TINCR can protect ATP citrate lyase (ACLY) from ubiquitin degradation to maintain total cellular acetyl-CoA levels. Accumulation of cellular acetyl-CoA promotes de novo lipid biosynthesis and histone H3K27 acetylation, which ultimately regulates the peptidyl arginine deiminase 1 (PADI1)-MAPK-MMP2/9 pathway, and then promoting NPC proliferation, metastasis and cisplatin resistance[93].

### Acquiring CSC properties

In recent years, cancer stem cells (CSC) have become one of the hot spots in cancer researches, and they are considered as the root of tumor growth, proliferation and recurrence[94, 95]. Previous reports indicate that CSCs, similar to embryonic stem cells (ESCs), have the abilities of self-renewal and self-differentiation[96]. These suggest that there may be common signal transduction pathways and molecular markers between CSCs and ESCs. lncRNAs are the necessary regulatory factors for many developmental pathways, including maintaining the pluripotency of stem cells, regulating apoptosis, generating red blood cells, and

differentiating horn cells[97, 98]. For NPC, several stem cell markers have been identified, such as Oct4, c-Myc, Sox2 and ALDH, which are believed to play a key role in the progression of NPC and chemoresistance[99]. Importantly, multiple signaling are involved in the maintenance of NPC stem cells, such as PI3K/Akt, Wnt- $\beta$ -catenin, JAK/STAT, and Hippo-YAP pathways[100]. The lncRNAs also participate in the regulation of CSC properties (Figure 3C). The lncRNA PVT1 promotes cancer stem like properties in NPC cells by inhibiting miR-1207 and activating PI3K/Akt signaling pathway[101]. Besides, a novel MACC1-AS1/miR-145/Smad2 negative loop responsible for NPC cell stemness. Chen et al. found that MACC1-AS1 act as a ceRNA to antagonize the activity of miR-145 which can target Smad2. In turn, Smad2 can bind to MACC1-AS1 promoter and increase MACC1-AS1 expression, forming a new MACC1-AS1/miR-145/Smad2 negative loop responsible for NPC cell stemness[102]. Transcriptional factor YAP is one of the executors of Hippo pathway which is a kinase cascade involving mammalian STE20-like protein kinase 1 (MST1) and the large tumor suppressor 1 (LATS1) and LATS2, in which YAP is phosphorylated and inactivated by LATS1/2[103]. Previous study has shown that YAP can confer stemness on tumor cells[104], and YAP has been considered as a "stemness factor" in several types of stem cells[105]. But the lncRNA THOR can attenuate the cisplatin sensitivity of NPC cells by enhancing cell stemness via promoting YAP transcriptional activity[59].

### Activating invasion and metastasis

Tumor metastasis leads to the vast majority of cancer-related deaths. In short, EMT and angiogenesis play major roles in tumor metastasis, including NPC. Epithelial-mesenchymal transition is a biological process involving the adhesion between cells, which is related to the migration of cancer cells. During the process, epithelial markers (E-cadherin, ZO-1, etc.) are down regulated, while mesenchymal markers (N-cadherin, vimentin, ZEB1, etc.) are up-regulated[106, 107]. lncRNAs also participate in it of NPC (Figure 3C). Such as the lncRNA MALAT1, it can be used as a competitive endogenous RNA (ceRNA) to competitively sponge with miR-124, thus releasing the inhibited target Capn4, which promotes the progress of NPC by reducing the expression of E-cadherin and increasing the expression of N-cadherin and vimentin[45]. As well as the lncRNA NEAT1, which regulates miR-204-mediated ZEB1 to promotes epithelial to mesenchymal transition and radioresistance through miR-204/ZEB1 axis in NPC[46]. In addition to miRNA sponge, lncRNAs can

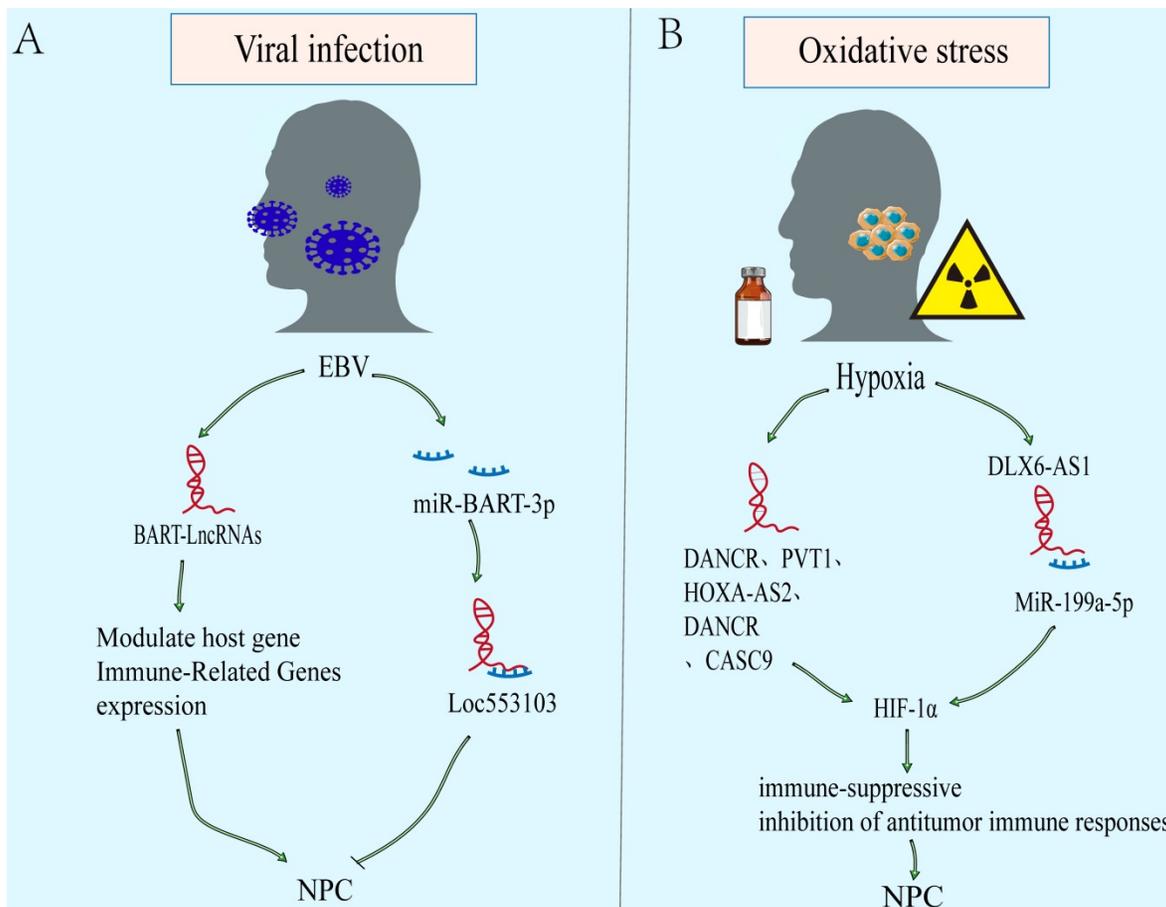
also directly regulate the expression of EMT related molecules, thus affecting the signaling pathway, including NF-κB, PI3K / Akt, MEK / ERK / c-Myc and Rho / RAC signaling pathway[108-111]. For example, the expression level of NKILA is enhanced in high metastatic cells than others. In mechanism, NKILA inhibited NF - κ B activation by suppressing IKK induced I κ B phosphorylation in NPC[111].

Angiogenesis is a key step in tumor development. And new angiogenesis is essential for the production of lethal tumor masses[112, 113]. In the development of tumor, pathological angiogenesis is driven by the overexpression of angiogenic factors including lncRNAs, which causes local imbalance between angiogenic and antiangiogenic factors, thus leading to the recruitment of new vascular supply (Figure 3D)[113, 114]. In NPC, the HOX transcript antisense RNA (HOTAIR) is found to activate the transcription of VEGF-A and up-regulate the expression of glucose regulated protein 78 (GRP78), then up-regulating the expression of VEGF-A and Ang2 to promote angiogenesis[115]. Therefore, blocking VEGF / VEGFR signal transduction to affect

vascular production and destroy nutrition and oxygen supply can provide treatment strategies[114, 116]. Another example is serine/arginine repetitive matrix protein 2-alternative splicing (SRRM2-AS), which exerts facilitating effects on angiogenesis in NPC via activating MYLK-mediated cGMP-PKG signaling pathway[117]. And angiostatin (caplostatin and endostatin) has been approved for the treatment of tumor and achieved good results[118].

**LncRNAs as a modulator of microenvironment associated with NPC**

Epstein Barr Virus infection and oxidative stress caused by multiple factors bring unique microenvironment to NPC. The EBV-encoded virus associated products can give NPC cells growth advantages in tumor microenvironment (TME) [119]. In addition, hypoxia microenvironment causing by many factors, such as drugs and radiotherapy, can activate the hypoxia signal pathway and affect the progress of NPC[120, 121]. Notably, the imbalance of lncRNAs is closely related to the EBV and hypoxia related microenvironment of NPC (Figure 4).



**Figure 4. LncRNAs as modulators of microenvironment associated with NPC. A.** EBV-encoded virus associated products can give NPC cells growth advantages in tumor microenvironment (TME). **B.** The oxidative stress microenvironment causing by many factors, such as drugs and radiotherapy, can activate the hypoxia signal pathway and affect the progress of NPC.

## Viral infection

EBV infection is an obvious feature of non-keratinizing NPC. The EBV-encoded viral products alter host cell signaling to facilitate tumor development and progression[122, 123]. Latent EBV exists only in tumor cell, mainly expressing EBV nuclear antigen 1 (EBNA1), EBV-encoded RNAs (EBERs), and elevated levels of BamHI-A rightward transcripts (BARTs) RNA[119, 124]. In addition, abnormal expression of lncRNAs is also found in EBV-infected. Evidences show that EBV can further regulate the downstream carcinogenic or tumor suppressor molecules via lncRNAs (Figure 4A). In NPC, EBV expresses few viral proteins but elevates levels of BARTs RNA, including viral microRNAs and lncRNAs[125-127]. And it also has long been suggested that EBV-infected NPC cells represents a unique TME. The lncRNA BART modulates host gene and immune-related genes expression, generates a cellular environment which supports EBV latency, and drives the oncogenic process[31, 128]. However, other than encoding oncogenes and promoting nasopharyngeal epithelium malignant transformation, some genes encoded by EBV can also inhibit the phenotype. However, there are few studies on the regulation of lncRNAs by EBV in NPC, and more evidence are needed to explain the mechanism.

## Oxidative stress

Most tumor cells are in a state of high metabolism and rapid proliferation. Besides, some factors, such as chemotherapy and radiotherapy, result in the continuous decline of oxygen content in the microenvironment. Eventually, a hypoxic microenvironment is often formed. However, tumor hypoxia is a significant factor leading to tumor treatment failure, recurrence and metastasis, due to the more aggressive ability of hypoxic tumor cells than normal oxygen cells[129]. Over the above process, hypoxia inducible factor-1  $\alpha$  (HIF-1  $\alpha$ ) plays an important role in survival of hypoxic tumor cells, including NPC[130, 131]. Compared with normal nasopharyngeal epithelium, HIF-1  $\alpha$  is overexpressed and associates with TNM stage, lymph node metastasis, distant metastasis, and poor prognosis of NPC[132]. The downstream effects of an enhanced HIF-1 $\alpha$  expression include (a) an activation of immune-suppressive effects (recruitment and stimulation of immune-suppressor cells [e.g., Treg, MDSC], and secretion of immune-suppressive TH2-type cytokines). And (b) inhibition of antitumor immune responses (including immune cell actions [e.g., NK, NKT, CD4+, CD8+], antigen-presenting cells [e.g., DC], and production of immune-stimulatory TH1-type cytokines)[133]. There

is increasing evidence to support that lncRNAs may take part in hypoxia regulation related cancer progression including NPC (Figure 4B)[39, 134, 135]. The DANCR is initially discovered to be a carcinogen in hepatocellular carcinoma (HCC)[136]. Bioinformatics analysis suggested that DANCR is related to NPC metastasis and hypoxia phenotype. Mechanistically, DANCR interacted with the RNA-binding protein NF90/NF45 complex to stabilize HIF-1  $\alpha$  mRNA, leading to NPC Hypoxia tolerance and metastasis[65]. In addition, lncRNAs such as PVT1, HOXA-AS2 and DLX6-AS1 are also found to regulate HIF-1  $\alpha$  expression[39, 134, 135].

## Diagnostic and therapeutic potentials of lncRNA in NPC

Up to now, MRI, CT and  $^{18}$ F-FDG-PET / CT are the most commonly used imaging methods for staging and curing NPC[137]. Yet, this kind of surveillance imaging is not enough to show early NPC. what's more, although EBV DNA testing can divide NPC patients into different risk subgroups, there is still lack of biomarkers with high specificity and sensitivity for NPC. Accordingly, emerging diagnostic and prognostic methods aim to increase accuracy in a more economical and non-invasive manner. In addition to the lack of reliable biomarkers, limited treatment options are also the causes of NPC related death. Although the survival rate of early NPC after radiotherapy and chemotherapy is high, the survival rate of patients with metastatic or recurrent NPC is still low. Therefore, new biomarkers and therapeutic targets are urgently needed to improve the diagnosis and treatment of NPC. Recently, the in-depth study of lncRNAs in NPC will provide new clinical utility for early diagnosis and treatment of NPC.

## lncRNAs are potential biomarkers for the diagnosis and treatment of NPC

lncRNAs are considered as a new biomarker of diseases. Many lncRNAs show species-specific and tissue-specific expression, which has potential applications in clinical oncology and become possible diagnostic biomarkers and predictors of therapeutic response.

As mentioned above, compared with normal nasal mucosa, there are a large number of unusual levels of lncRNAs in NPC tissues, which are helpful to distinguish NPC patients from normal people. The Genome sequencing showed that 306 lncRNAs are up-regulated, while 204 lncRNAs are down regulated[138]. Although only a few known lncRNAs have function annotation. These differentially expressed lncRNAs have potential to be new

biomarkers of NPC. Like linc00312, the ROC curve showed that the level of linc00312 can distinguish NPC patients from non-tumor patients, with a sensitivity of 72.1% and a specificity of 87.7%, suggesting that linc00312 could be a potential biomarker for diagnosis of NPC[139].

Circulating or secretory lncRNAs can also play important roles in clinical diagnosis[140]. Compared with solid tumor tissue sampling, liquid biopsy is an ideal non-invasive diagnostic method. Importantly, there may be multiple NPC related lncRNAs in body fluids (circulating lncRNAs). In the serum circulation of NPC patients, lncRNA MALAT1, APAF1-AS1 and AL359062 are markedly up-regulated and correlated with poor prognosis, indicating that they can be used as biomarkers for predicting poor outcome of NPC[141]. Representative NPC promoted lncRNAs can be detected in blood samples, and can be easily quantified by traditional qPCR[142], which suggests a non-invasive method for the diagnosis of NPC by circulating lncRNAs detection.

Of course, various lncRNAs may also be potential prognostic markers for NPC. The lncRNA ANRIL is also an independent prognostic biomarker for local recurrence of NPC patients, which is higher in patients in stage III - IV than in stage I - II[87]. Not surprisingly, lncRNAs are involved in tumor metastasis may have good prognostic value. Higher linc01420 is apparently associated with distant metastasis and lower overall survival of NPC[143].

lncRNAs play a vital role in the treatment of NPC. It indicates good anti-cancer effect by regulating their functions, which means that it may become a new target of NPC treatment. Like knockout of MINCR and PTPRG-AS1, which can enhance the sensitivity of NPC to X-ray[144, 145]. The MRV11-AS1 can increase paclitaxel chemosensitivity of NPC by modulating the Hippo-TAZ signaling pathway[146]. The LINC00346 regulates the cisplatin resistance of NPC cells by inhibiting miR-342-5p, which could provide a potential target for chemotherapy resistance[147]. Although ARHGAP42 protein in metastatic NPC is obviously higher than that in primary NPC, the silence of its antisense lncRNA uc010rul resulted in decreased ARHGAP42 and significant inhibition of NPC migration and invasion[148]. Furthermore, potential role of lncRNA GAS5 polymorphisms rs2067079 and rs6790 as predictive biomarkers for chemoradiotherapy induced toxic reactions in NPC patients[149].

### **lncRNAs as promising NPC therapeutic targets**

So far, the prognosis of advanced NPC still needs to be improved. Although PD-L1 has been used in the

treatment of advanced NPC, the efficacy still needs further observation. Hence, the new goal is necessary to improve the prognosis of NPC. RNA-based therapeutics against cancer has gradually changed from concept to reality. The key role of lncRNAs in NPC makes it possible to become a new drug target for therapeutic interventions. These methods of targeting lncRNA mainly include antisense oligonucleotides (ASO) and RNA interference (RNAi), both of which show good anticancer activity by targeting lncRNAs.

Antisense oligonucleotides, a single strand DNA of 15-20 nucleotides, which can recognize specific sequences and degrade lncRNA by RNase-H[150]. They bind to RNA via standard Watson-Crick base pairing. After binding with target RNA, gene expression can be inhibited or changed by steric hindrance, splicing change, target degradation initiation or other events[151]. Currently, ASOs targeting different mRNAs have entered into clinical trials for several diseases including cancer[151], emerging as a promising therapeutic approach for targeting lncRNAs[152]. Moreover, in order to achieve RNase H-mediated knockdown of target RNAs, chimeric ASOs referred to as 'GapmeRs' are used. GapmeR ASOs are RNA-DNA-RNA hybrids, which allows RNase H-mediated target RNA to extend and cleave in the center of DNA, while increasing target affinity and resistance to nuclease activity[153]. In NPC, knocking down of BART RNA is achieved by targeting it for GapmeR-mediated RNase H cleavage to disrupt its function, and successfully decreasing the level of BART, thus inhibiting immune evasion, progression, and metastasis of NPC[31].

The siRNA is a double stranded RNA with 19-30 nucleotides. It can complementally bind to lncRNAs sequence through RNA mediated silencing complex (RISC) to degrade target lncRNAs[154]. Nevertheless, the preclinical study of targeting lncRNA with siRNAs / shRNA is very limited. And in the research of Li et al. the intracellular level of lncRNA-ROR is degraded after transcription with siRNA ROR. As a result, it can inhibit the proliferation and migration of NPC and improve the chemical resistance[155].

### **Conclusions**

With the deep research, lncRNAs are thought to be a new frontier for many diseases including malignant tumors. So that, A detailed understanding of their expression and mechanisms of action are critical in order to appreciate the importance of this unique class of molecules. Remarkably, the fact that lncRNAs are generally expressed in a cell- or tissue-specific manners make them to be exceptional

therapeutic targets. Although many questions and challenges remain to be addressed, sequence-based nucleic acid therapeutics are evolving at a rapid pace. Identification and evaluation of a lncRNA target in the context of cancers may be translated into clinical scenarios in a reasonable time window.

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## Author Contributions

SQF and WYW designed the research. HHW drafted the manuscript. SQF and WYW improved the structure of this manuscript and completed the diagrams. HHW and WYW discussed and revised the manuscript. All authors read and approved the final manuscript.

## Competing Interests

The authors have declared that no competing interest exists.

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